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A haemodynamic and radionuclide assessment of diltiazem in coronary heart disease

B. SILKE, S. K. SHARMA, S. P. VERMA, K. A. MIDTBO, G. REYNOLDS & S. H. TAYLOR
University Department of Cardiovascular Studies, The General Infirmary at Leeds, Leeds

1 To obtain multiple dose-response haemodynamic and radionuclide data on i.v. diltiazem, 12 ischaemic patients were studied during routine catheterization.

2 At rest, following a 20 min stable control period, the effects of four doses (0.0625, 0.0625, 0.125 and 0.25 mg kg^{-1} diltiazem at 5 min intervals) were measured in the 3–5 min following i.v. injection. The exercise effects of the cumulative 0.5 mg kg^{-1} dosage were assessed by comparing a control and post drug period of supine bicycle exercise.

3 The increase in plasma diltiazem levels correlated linearly with the administered dose and achieved therapeutic levels. There were significant dose-related reductions in systemic arterial blood pressure and vascular resistance index; the heart rate fell and cardiac stroke index increased. The calculated double-product (heart rate × systolic blood pressure) was significantly reduced. The left ventricular filling pressures, ejection fraction and cardiac volumes were unaltered.

4 During supine bicycle exercise, the systemic diastolic blood pressure, heart rate and calculated double-product were reduced without change in other parameters.

5 Over the dose range 0.0625–0.5 mg kg^{-1}, diltiazem acutely increased cardiac stroke index and reduced resting heart rate. These haemodynamic data, taken together with its described coronary vasodilator activity suggest that its role in acute vasospastic angina and during angiographic procedures ought to be explored further.

Keywords diltiazem coronary heart disease

Introduction

The efficacy of slow-calcium channel blocking compounds in the clinical therapy of angina pectoris is established; relief of clinical symptoms and improvement in treadmill time to angina has been demonstrated in controlled clinical studies (Atterhog *et al.*, 1975; Weiner *et al.*, 1983). The effectiveness of this form of therapy approaches that of β-adrenoceptor blocking agents in the ability to reduce angina (Arnman & Ryden, 1982; Subramanian, 1983). Their mechanism of anti-anginal action is complex and incompletely understood; important factors may be a fall in systemic vascular resistance, with a reduced left ventricular afterload, together with augmented myocardial blood flow (Singh, 1982; Stone *et al.*, 1980). However, it is clear that slow-calcium channel blockade is usually accompanied by improved indices of cardiac function in man (Kieval & Myerburg, 1982; Ellrodt *et al.*, 1980).

Diltiazem, a 1,5-benzothiazepine derivative, has a pharmacodynamic profile similar to verapamil (Ellrodt *et al.*, 1980); numerous clinical studies have confirmed its anti-anginal efficacy during chronic administration (Subramanian, 1983; Hossack *et al.*, 1981). Its intravenous use in acute situations has received less attention.

Correspondence: Dr B. Silke, The General Infirmary at Leeds, Leeds LS1 3EX

Although the haemodynamic effects of single i.v. doses of diltiazem, have been described in coronary artery disease (Legrand *et al.*, 1984), the multiple dose-response effects on systemic haemodynamics, relevant to dosage considerations for acute intravenous applications, have not been previously described. This study also assessed the acute actions of diltiazem on rest and exercise left heart volumes, pressure and pumped output allowing a global assessment of cardiac performance at rest and during exercise.

Study design

The study was a single-blind haemodynamic and radionuclide evaluation of the effects of intravenous diltiazem. Patients were studied fasting without premedication. Prior to the definitive study, patients were familiarised with the technique of supine-bicycle exercise, and the maximum work-load which each could maintain for 4 min determined; the chosen workload reliably induced angina between 2–4 min of exercise. In each patient the study commenced (15–30 min after blood pool labelling) with the control 4 min supine bicycle exercise at the individually predetermined constant workload. Haemodynamic and radionuclide measurements were obtained minute by minute. Following circulatory restabilisation (20 min), the control studies at rest were undertaken over 20 min. Four sets of haemodynamic and radionuclide measurements were made in the 3–5 min following each of four injections of 10 ml saline into the pulmonary artery. Diltiazem was then administered by i.v. injection (each bolus over 1 min) in doses of 0.0625, 0.0625, 0.125 and 0.25 mg kg^{-1} at consecutive 5 min intervals; haemodynamics and radionuclide measurements being recorded in the 3–5 min following each injection. Patients were immediately reexercised at the same workload and measurements repeated in an identical manner.

Patients

Twelve male patients with electrocardiographic and angiographic evidence of coronary artery disease and chronic stable angina pectoris were studied during diagnostic evaluation prior to coronary bypass artery grafting. Their average age was 51 ± 2 (range 46–65 years); 11 had a history of myocardial infarction (6 inferior; 5 anterior) > 6 months prior to these investigations. None of the patients had radiographic cardiomegaly (cardiothoracic ratio 0.47 ± 0.01) or pulmonary venous congestion. The angiographically determined left ventricular ejection fraction was 52 ± 2%; angina duration was 13 ± 5 months. Coronary artery stenosis (i.e. > 70% narrowing) was present in 1, 2 or 3 vessels in 1, 8 and 3 respectively. Six of the patients had a scar clearly evident on LV angiography with depressed, dyskinetic or absent wall motion in the affected region; three others had an abnormal contractile pattern (dyskinesia or early systolic relaxation) and one an antero-apical aneurysm; two had relatively normal angiographic LV appearances. The resting ejection fraction was 51 ± 2 and fell to 38 ± 3 by 4 min supine bicycle exercise, at an exercise workload of 107 ± 17 watt (range 30–175). Excluded from the study were patients with unstable angina, a myocardial infarction within the previous 3 months and those previously receiving sustained therapy with cardioactive medications (with the exception of nitrates). The purpose of the study was explained to each patient who freely consented to participate; the study was approved by the Hospital Ethics Committee.

Haemodynamic procedures

A narrow bore (7F) Swan-Ganz thermodilution catheter was introduced percutaneously via a median basilic approach in the brachial fossa and advanced into the pulmonary circuit under wave form monitoring control. Systemic arterial pressure was externally transduced via a cannula (Vygon 1.2 mm external diameter) inserted with the Seldinger technique into the brachial artery. Both pulmonary and systemic pressures were externally transduced (Bell & Howell 4-327-I), zero reference being at mid-chest (average 10 cm) distance below the horizontal plane of the sternal angle; both pressures were continuously displayed (Simonson & Weel System 8000) and recorded together with the ECG on a high performance ultra-violet recorder (EMI SE 6300). Pressures were averaged blind by an observer not involved in their acquisition from 30–60 s traces obtained with the recorder run at 30 cm min^{-1}. Cardiac output was via the thermodilution technique, injection (aspirated via three-way tap from a reservoir at 0° C) of the indicator (10 ml dextrose-saline) was with a CO_2 powered gun (OMP 3700); cardiac output being automatically computed and recorded (Gould Statham Computer SP 1425/Recorder SP 2009). The variance of this technique in our laboratory is < 6% at rest and < 7% during steady state bicycle exercise. Systemic vascular resistance, stroke volume and left ventricular stroke work were derived from the following formulae and corrected for body surface area:

1. systemic vascular resistance index = mean arterial pressure (MAP) × 80/cardiac index
2. stroke volume index (SVI) = cardiac index/heart rate
3. left ventricular stroke work index = SVI × (MAP-PAOP) × 0.0136

Radionuclide techniques

The radionuclide studies were undertaken using an ECG-triggered, microprocessor based, non-imaging nuclear probe (Nuclear Stethoscope, Bios Inc., Valhalla, New York), employing previously described techniques (Wagner, 1982; Strashun *et al.*, 1981). Patients were injected with 15 mg stannous pyrophosphate (TechneScan PYP kit, Mallinckrodt Diagnostic Products), and 30 min later with red blood cells labelled *in vitro* with 99m-technetium (15 mCi). For each study, the nuclear stethoscope was positioned paralled to the catheter table and at 90 cm distance from the midpoint of the sternal angle. The degree of obliquity and caudal tilt to yield an optimum assessment was determined (usually 20–35 degree LAO with a 10–20 degree caudal tilt). The circumference of the probe was traced with an indelible marker on the chest to allow the investigator to always retain the same position; rest and exercise studies were undertaken using techniques to minimise chest movement. All angulations, and probe/chest position were subsequently maintained constant. The area of maximal left ventricular count activity and level of background activity were determined prior to each study using the microprocessor algorithm incorporated in the nuclear probe. Data were acquired in the ECG-gated mode for between 30 and 60 s, to a minimum of 10,000 counts. The left ventricular ejection fraction was determined from the displayed background substracted left ventricular time-activity curves. This technique has been calibrated in our laboratory; in 20 patients, in whom 10 consecutive resting ejection fractions were determined at 2 min intervals, the average variability was 3.5% (range 0.9–5.7%), and over six determinations during steady state bicycle exercise was 4.6% (range 1.0–11.2).

Left ventricular end-diastolic and end-systolic volume indices were determined from simultaneous ejection fraction and thermodilution stroke output determinations using the equations:

1. ejection fraction = stroke volume index/end-diastolic volume index
2. stroke volume index = end-diastolic volume index/end-systolic volume index

Plasma diltiazem determinations

Plasma diltiazem concentration was determined by a sensitive and specific gas chromatographic technique (Rovei *et al.*, 1977); the assay is linear over the measured range with coefficient of variation 4.4%; the lower limit of sensitivity is 4 ng ml^{-1}.

Statistical analysis

The rest and exercise data were evaluated by analysis of variance of repeated measurements (Dixon & Brown, 1979). The significance of difference between control and post-drug data was determined from the single value generated with a multiple comparison procedure (Winer, 1977). All values were judged significant at the conventional level (5%). The baseline haemodynamic variables were analysed for trends of change over the four resting control measurements; none being present the control data have been averaged from the four separate determinations.

Results

These studies were uneventful; no patient complained of adverse reactions. Although these studies were not undertaken with a view to symptomatic assessment, when asked whether there was any appreciable difference between the control and drug studies, eight stated that the severity of perceived angina was less during the drug period.

Stability of baseline control haemodynamic data

The stability of the baseline control data was adequately demonstrated from the small coefficients of variation of the control measurements. The average and range of the coefficients of the variation during the control period were: systolic blood pressure 2.1% (range 1.3–3.7%), diastolic blood pressure 1.9% (range 0.7–4.2%), mean blood pressure 1.6% (range 0.0–4.5%), heart rate 2.9% (range 1.2–4.6%), pulmonary artery occluded pressure (PAOP) 5.8% (range 0.0– 15.2%), cardiac index 3.1% (range 1.4%–7.3%) and left ventricular ejection fraction 2.1% (range 0.9–4.3%).

Plasma diltiazem measurements

The plasma diltiazem concentrations determined at the same time as each set of haemodynamic measurements were 39.5 ± 8.9 ng ml^{-1}

(mean ± s.e. mean), 39.5 ± 2.9 ng ml^{-1}, 87.7 ± 6.7 ng ml^{-1} and 142.3 ± 13 ng ml^{-1}, 3–5 min following the respective cumulative doses of 0.0625, 0.125, 0.25 and 0.5 mg kg^{-1} i.v. diltiazem. There was a significant correlation between the dose administered and the plasma concentration determined at each time ($r = 0.65$, $P < 0.0001$).

Effects at rest (Figure 1, Table 1)

Over the administered diltiazem dosage range, there were significant reductions in systemic systolic, diastolic and mean arterial blood pressure and systemic vascular resistance index. The heart rate was reduced without change in the cardiac index, PAOP, left ventricular ejection fraction or cardiac volumes. The left ventricular stroke volume index was increased. There was a highly significant ($P < 0.01$) and dose related reduction in double-product (10404 ± 507 control: to 9883 ± 549, 9614 ± 569, 9296 ± 495 and 9032 ± 522).

Effects during dynamic exercise (Table 2)

At the same workload, as in the control (drug free) period, the diastolic blood pressure, heart rate and systemic vascular resistance index were reduced without change in the PAOP or cardiac index. The exercise left ventricular ejection fraction, end-diastolic and end-systolic volumes were unchanged. The double-product was reduced. (24014 ± 2132 to 21949 ± 2353: −9.7%; $P = 0.005$).

Discussion

Although the efficacy of diltiazem in chronic stable angina has been well documented in chronic stable angina studies, the multiple i.v. dose response effects of the drug have not been previously described. In the current study, the haemodynamic and radionuclide effects of diltiazem (0.0625–0.5 mg kg^{-1}) were assessed in patients with chronic stable angina pectoris. The study

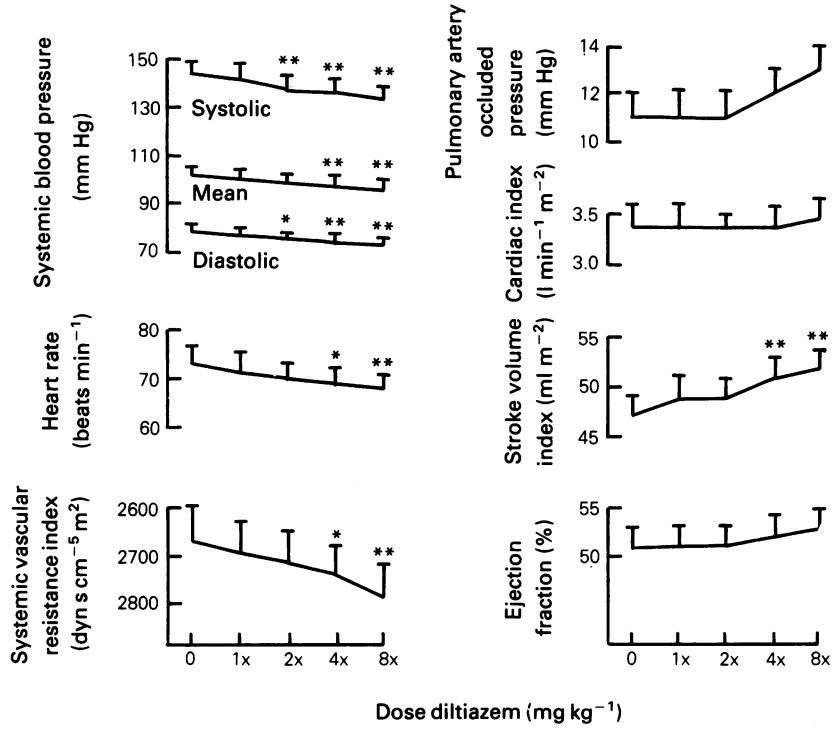

Figure 1 Haemodynamic dose-response effects (mean ± s.e. mean) of i.v. diltiazem on cardiac parameters in coronary artery disease. Statistics represent differences from control. *$P < 0.005$, **$P < 0.01$. x = 0.0625 mg kg^{-1}.

Table 1 Haemodynamic effects of diltiazem at rest (mean ± s.e. mean). Cumulative dose of diltiazem (x = 0.0625 mg kg^{-1})

	Control	*1x*	*2x*	*4x*	*8x*
Systolic blood pressure (mm Hg)	144 ± 5	141 ± 5	137 ± 5**	136 ± 5**	133 ± 5**
Diastolic blood pressure (mm Hg)	78 ± 3	76 ± 2	75 ± 2*	73 ± 3**	72 ± 3**
Mean blood pressure (mm Hg)	102 ± 3	100 ± 3	99 ± 3	97 ± 3**	95 ± 4**
Heart rate (beats min^{-1})	73 ± 4	71 ± 4	70 ± 3	69 ± 3*	68 ± 3**
Pulmonary artery occluded pressure (mm Hg)	11 ± 1	11 ± 1	11 ± 1	12 ± 1	13 ± 1
Cardiac index (l min^{-1} m^{-2})	3.4 ± 0.2	3.4 ± 0.2	3.4 ± 0.1	3.4 ± 0.2	3.5 ± 0.2
Systemic vascular resistance (dyn s cm^{-5} m^2)	2475 ± 161	2411 ± 147	2372 ± 136	2320 ± 138*	2228 ± 126**
Stroke volume index	47 ± 2	49 ± 2	49 ± 2	51 ± 2**	52 ± 2**
Ejection fraction (%)	51 ± 2	51 ± 2	51 ± 2	52 ± 2	53 ± 2

Levels of significance relate to differences from control: $*P < 0.05$, $**P < 0.01$.

Table 2 Haemodynamic effects of diltiazem (cumulative dose 0.5 mg kg^{-1}) during dynamic exercise (mean ± s.e. mean)

		Rest	*Exercise time (min)* 1	2	3	4
Systolic blood pressure (mm Hg)	C	144 ± 5	187 ± 9	196 ± 10	200 ± 10	202 ± 10
	D	133 ± 5**	182 ± 8	193 ± 10	195 ± 10	196 ± 11
Diastolic blood pressure (mm Hg)	C	78 ± 3	92 ± 3	92 ± 3	91 ± 3	90 ± 3
	D	72 ± 3**	85 ± 3**	87 ± 3**	86 ± 3**	85 ± 3**
Mean blood pressure (mm Hg)	C	102 ± 3	123 ± 5	127 ± 5	128 ± 5	127 ± 5
	D	95 ± 4**	119 ± 5	123 ± 5*	123 ± 5	123 ± 5
Heart rate (beats min^{-1})	C	73 ± 4	107 ± 5	113 ± 6	118 ± 7	118 ± 7
	D	68 ± 3**	102 ± 5**	107 ± 6**	109 ± 7**	110 ± 7**
Pulmonary artery occluded pressure	C	11 ± 1	22 ± 2	24 ± 2	25 ± 2	25 ± 2
	D	13 ± 1	21 ± 2	22 ± 2	22 ± 2	22 ± 2
Cardiac index (l min^{-1} m^{-2})	C	3.4 ± 0.2	6.1 ± 0.4	6.6 ± 0.5	6.7 ± 0.5	6.9 ± 0.5
	D	3.5 ± 0.2	5.5 ± 0.3**	6.3 ± 0.4	6.5 ± 0.3	6.8 ± 0.5
Systemic vascular resistance (dyn s cm^{-5} m^2)	C	2475 ± 161	1703 ± 127	1607 ± 119	1588 ± 112	1544 ± 105
	D	2228 ± 126**	1775 ± 115	1635 ± 121	1560 ± 105	1517 ± 115
Stroke volume index (ml m^{-2})	C	47 ± 2	56 ± 2	59 ± 3	57 ± 3	58 ± 2
	D	52 ± 2**	55 ± 1	59 ± 2	61 ± 2	62 ± 2
Ejection fraction (%)	C	51 ± 2	42 ± 3	40 ± 3	39 ± 3	38 ± 3
	D	53 ± 2	41 ± 2	39 ± 3	40 ± 3	38 ± 3

C = Control
D = Diltiazem
Levels of significance relate to differences from control: $*P < 0.05$, $**P < 0.01$.

population was homogenous; all had confirmed coronary artery disease with angiographic and haemodynamic evidence of left ventricular dysfunction. The test situation has been previously validated; it has reliably described the acute pharmacodynamic activity of several slow-calcium channel blocking agents (Silke *et al.*, 1984a,b, 1985) in similar patients. The diltiazem regimen resulted in plasma concentrations which increased linearly with the administered dosage; previous work has demonstrated that steady-state therapeutic levels of diltiazem usually lie between 100 and 300 ng ml^{-1} (Hermann & Morselli, 1985). The stability of the baseline control period was amply demonstrated in the pre-drug 20 min period; the haemodynamic variability during repetitive exercise, at submaximal exercise, has previously been reported (Verma *et al.*, 1984).

The measurement techniques for the computerised measurement of blood flow and cardiac index by thermodilution have been well documented (Forrester *et al.*, 1972; Hoel, 1978; Sorenson *et al.*, 1976); in our laboratory the variability of cardiac index by this technique is $< 6\%$ at the rest and $< 7\%$ during constant load supine bicycle exercise. The left ventricular ejection fraction data was obtained with a non-imaging nuclear probe in the ECG multiple-gated mode. Several groups of investigators have validated this methodology (Strashun *et al.*, 1981; Bacharach *et al.*, 1977; Berger *et al.*, 1981). The reproducibility of this technique in our laboratory is good (i.e. rest $< 4\%$; exercise $<6\%$). There is also good correlation between the nuclear probe-derived and angiographically determined ejection fraction in our laboratory ($r = 0.84$, $P < 0.0001$); other investigators have demonstrated the accuracy of the technique, compared with the standard gamma camera ejection fractions in normal volunteers, both at rest and peak exercise (Lahiri *et al.*, 1984). Since ejection fraction is the ratio of stroke volume to end-diastolic volume, left ventricular end-diastolic volume index can be derived from simultaneously measured stroke volume index and ejection fraction. The left ventricular volumes calculated at rest and during dynamic exercise in the present series were similar to those derived by conventional gamma camera and biplane cineangiography techniques in patients with equivalent coronary artery disease (Rackley *et al.*, 1970; Field *et al.*, 1972; Links *et al.*, 1982; McKay *et al.*, 1984).

In our patients, the resting effects of diltiazem were dose-related reductions in systemic arterial pressure and vascular resistance index; heart rate fell without change in cardiac output or left ventricular filling pressure. During constant load bicycle exercise the major determinants of myocardial oxygen requirements (systemic arterial pressure and heart rate) were reduced without change in cardiac index or left ventricular filling pressure. Diltiazem did not alter either rest or exercise left ventricular ejection fraction. Beneficial cardiovascular actions are suggested in that cardiac double-product was reduced at unchanged filling volume, although these would require further substantiation. The reduction in heart rate occurred despite a fall in systemic vascular resistance which might have been expected to increase heart rate due to reflex sympathetic stimulation. The depressant effect of diltiazem on sino-atrial node automaticity (Kawai *et al.*, 1981), however, probably prevented the expected reflex tachycardia which is frequently observed with nifedipine (Nelson *et al.*, 1984), nicardipine (Silke *et al.*, 1984b), and nisoldipine (Silke *et al.*, 1985) in coronary artery disease.

Our results can be compared with other data on diltiazem. Legrand *et al.* (1984) in coronary patients after 0.5 mg kg^{-1} i.v. diltiazem demonstrated decreases in systemic blood pressure, vascular resistance and exercise pulmonary capillary wedge pressure; there was a small increase in cardiac index. Total exercise duration and time to ischaemia were prolonged. The plasma levels correlated with the increase in double product, suggesting a concentration related improvement of myocardial oxygen supply as found by others (Bourassa *et al.*, 1980; Franklin *et al.*, 1980). Joyal *et al.* (1986) in 14 patients with chronic stable angina pectoris on a 250 $\mu g\ kg^{-1}$ i.v. bolus plus 1.4 $\mu g\ kg^{-1}\ min^{-1}$ infusion, noted significant correlation between blood pressure reduction and plasma diltiazem concentrations. The fall in systemic resistance resulted in a transiently increased heart rate; the stroke index was augmented at unchanged left ventricular volume and contractility indices. Bourassa *et al.* (1980) showed significant coronary vasodilation following diltiazem in patients with proven coronary obstruction with a variable effect on myocardial oxygen requirements. Moreover a heart rate reduction was negatively correlated with the extent of the fall in haemodynamic systemic vascular resistance. Cardiac performance and left ventricular end diastolic pressure were unaltered. Diverging from these results, Hossack *et al.* (1982) in patients with exercise-induced angina, 1 h following a single oral dose of 120 mg, found a pronounced decrease in mean pulmonary capillary pressure during exercise compared with control, provided pretreatment pressure exceeded 16 mm Hg. They also observed a

significant increase in exercise cardiac output, neither of which were reproduced in our study. Petru *et al.* (1983) reported a 4% increase in resting and an 8% in exercise ejection fraction in patients with coronary artery disease unlike the absence of change in our patients.

The haemodynamic profile of diltiazem can be cautiously compared with other slow-calcium channel blocking agents studied in demographically and haemodynamically similar patients and using equivalent pharmacodynamic doses of each drug (Nelson *et al.*, 1984; Silke *et al.*, 1984a,b, 1985). Diltiazem appears haemodynamically different from the predominantly selective arteriolar vasodilator calcium blockers, nifedipine, nicardipine and nisoldipine, but similar to verapamil, in terms of effects on left ventricular function. Unlike the dihydropyridines, diltiazem acutely did not increase heart rate consequent on the induced hypotension; in this regard it resembles verapamil.

These data, suggest that diltiazem i.v. is safe even in patients with left ventricular functional impairment due to coronary artery disease. Over the dose range there was no change in ejection fraction, a modest increase in cardiac stroke output and a reduced calculated double-product. As calcium channel blockers, due to their coronary vasodilator and metabolic actions are increasingly utilized in the management of unstable angina (Stone *et al.*, 1980; Dargie *et al.*, 1981), our data suggest that the lack of tachycardia following diltiazem might make it useful for this application. Kimura & Kishida (1981) reviewed the efficacy of diltiazem in variant angina; a 91% response rate was reported similar to nifedipine (94%) and verapamil (86%). Schroeder and colleagues (1982) reported a 94% reduction in angina frequency in 36 patients with variant angina. Diltiazem has also been shown to increase total coronary blood flow and dilate major coronary arteries in the experimental animal and in man (Bourassa *et al.*, 1980); this augmentation appears dose-dependent—0.05 mg kg^{-1} increased flow by 23% compared with 47% following 0.15 mg kg^{-1} (Bertrand *et al.*, 1982). These data suggest possible uses during coronary angiographic or angioplasty procedures. Certainly our data provides an encouraging basis for further exploration of its value in the acute management of cardiovascular disease.

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References

Arnman, K. & Ryden, L. (1982). Comparison of metoprolol and verapamil in the treatment of angina pectoris. *Am. J. Cardiol.*, **49**, 821–827.

Atterhog, J. H., Ekelund, L. G. & Myelin, A. L. (1975). Effect of nifedipine on exercise tolerance in patients with angina pectoris. *Eur. J. clin. Pharmac.*, **8**, 125–130.

Bacharach, S. L., Green, M. V., Borer, J. S., Ostrow, H. G., Redwood, D. R. & Johnston, G. S. (1977). ECG-gated scintillation probe measurement of left ventricular function. *J. nucl. Med.*, **18**, 1176–1183.

Berger, H. J., Davies, R. A., Batsford, W. P., Hoffer, P. B., Gottschalk, A. & Zaret, B. L. (1981). Beat to beat left ventricular performance assessed from the equilibrium cardiac blood pool using a computerized nuclear probe. *Circulation*, **63**, 133–142.

Bertrand, M. E., Dupuis, B. A., Lablanche, J. M., Tilmant, P. Y. & Thieuleux, F. A. (1982). Coronary haemodynamics following intravenous or intracoronary injection of diltiazem in man. *J. cardiovasc. Pharmac.*, **4**, 695–699.

Bourassa, M. G., Cote, P., Theroux, P., Tuban, J. F., Genain, C. & Waters, D. D. (1980). Haemodynamics and coronary flow following diltiazem administration in anesthetized dogs and humans. *Chest*, **78** (suppl), 224–230.

Dargie, H., Rowland, E. & Krikler, D. (1981). Role of calcium antagonists in cardiovascular therapy. *Br. Heart J.*, **46**, 8–16.

Dixon, W. J. & Brown, M. B. (1979). (eds) *Biomedical computer programs 'P' series*, pp. 540–580. Berkeley: University of California Press.

Ellrodt, G., Chew, C. Y. C. & Singh, B. (1980). Therapeutic implications of slow calcium blockade in cardio-circulatory disorders. *Circulation*, **60**, 669–678.

Field, B. J., Russell, R. O., Jr, Dowling, J. T. & Rackley, C. E. (1972). Regional left ventricular performance in the year following myocardial infarction. *Circulation*, **46**, 679–689.

Forrester, J. S., Ganz, W., Diamond, G. A., McHugh, T. J., Chonette, D. & Swan, H. J. C. (1972). Thermodilution cardiac output determination with a single flow directed catheter. *Am. Heart J.*, **83**, 306–311.

Franklin, D., Millard, R. W. & Nagao, T. (1980). Responses of coronary collateral flow and dependent myocardial mechanical function to the calcium antagonist, diltiazem. *Chest*, **78** (suppl), 200–204.

Hermann, P. & Morselli, P. L. (1985). Pharmacokinetics of diltiazem and other calcium entry blockers. *Acta Pharmac. Tox.*, **57** (Suppl 2), 10–20.

Hoel, B. L. (1978). Some aspects of the clinical use of thermodilution in measuring cardiac output. With

particular reference to the Swan-Ganz thermodilution catheters. *Scand. J. clin. lab. Invest.*, **48**, 383–388.

Hossack, K. F., Bruce, R. A., Ritterman, J. B., Kusumi, F. & Trimble, S. (1982). Divergent effects of diltiazem in patients with exertional angina. *Am. J. Cardiol.*, **49**, 538–546.

Hossack, K. F., Bruce, R. A., Trimble, S. & Kusumi, F. (1981). Improved exercise peformance in patients with stable angina pectoris receiving diltiazem. *Am. J. Cardiol.*, **47**, 95–101.

Joyal, M., Pieper, J., Cremer, K., Feldman, R. L. & Pepine, C. J. (1986). Pharmacodynamic aspects of intravenous diltiazem administration. *Am. Heart J.*, **111**, 54–61.

Kawai, C., Konishi, T., Matsuyama, E. & Okazaki, H. (1981). Comparative effects of three calcium antagonists, diltiazem, verapamil and nifedipine on the sino-atrial and atrioventricular nodes. *Circulation*, **63**, 1035–1042.

Kieval, J. & Myerburg, R. J. (1982). The hemodynamic effects of calcium channel blocking agents. A brief review. *Angiology*, **33**, 516–521.

Kimura, E. & Kishida, H. (1981). Treatment of variant angina with drugs: a survey of 11 cardiology institutes in Japan. *Circulation*, **63**, 844–848.

Lahiri, A., Bowles, M. J., Jones, R. I., Crawley, J. C. W. & Raftery, E. B. (1984). Assessment of left ventricular function in coronary artery disease with the nuclear probe during intervention studies. *Br. Heart J.*, **52**, 422–430.

Legrand, V., Hastir, F., Vandormael, M., Collignon, P. & Kulbertus H. E. (1984). Haemodynamic effects of intravenous diltiazem at rest and exercise in patients with coronary artery disease. *Eur. Heart J.*, **5**, 456–463.

Links, J. M., Becker, L. C., Shindledecker, J. G., Guzman, P., Burrow, R. D., Nickoloff, E. L., Alderson, P. O. & Wagner, H. N. (1982). Measurement of absolute left ventricular volume from gated blood pool studies. *Circulation*, **65**, 82–91.

McKay, R. G., Aroesty, J. M., Heller, G. V., Royal, H., Parker, J. A., Silverman, K. J., Kolodny, G. M. & Grossman, W. (1984). Left ventricular pressure-volume diagrams and end-systolic pressure-volume relations in human beings. *J. Am. Coll. Cardiol.*, **3**, 301–312.

Nelson, G. I. C., Silke, B., Ahuja, R. C., Hussain, M., Forsyth, D. & Taylor, S. H. (1984). The effect on left ventricular performance of nifedipine and metoprolol singly and together in exercise-induced angina pectoris. *Eur. Heart J.*, **5**, 67–79.

Petru, M. A., Crawford, M. H., Sorenson, S. G., Chaudhuri, T. K., Levine, S. & O'Rourke, R. A. (1983). Short and long term efficacy of high-dose oral diltiazem for angina due to coronary artery disease: a placebo-controlled, randomised, double-blind crossover study. *Circulation*, **68**, 139–147.

Rackley, C. E., Dean, H. D., Baxley, W. A., Jones, W. B. & Dodge, H. T. (1970). Left ventricular chamber volume, mass and function in severe coronary artery disease. *Circulation*, **41**, 605–613.

Rovei, V., Mitchard, M. & Morselli, P. L. (1977). Simple, sensitive and specific gas chromatographic method for the quantitation of diltiazem in human body fluids. *J. Chromatogr.*, **138**, 391–398.

Schroeder, J. S., Lamb, I. H., Ginsburg, R., Bristow, M. R. & Hung, J. (1982). Diltiazem for long-term therapy of coronary arterial spasm. *Am. J. Cardiol.*, **49**, 533–537.

Silke, B., Frais, M. A., Muller, P., Verma, S. P., Reynolds, G. & Taylor, S. H. (1985). Haemodynamic dose-response effects of nisoldipine in coronary artery disease. *Br. J. clin. Pharmac.*, **20**, 675–680.

Silke, B., Verma, S. P., Ahuja, R. C., Nelson, G. I. C., Hussain, M. & Taylor, S. H. (1984a). Haemodynamic dose-response effects of intravenous verapamil in coronary artery disease. *Herz*, **9**, 353–361.

Silke, B., Verma, S. P., Nelson, G. I. C., Hussain, M. & Taylor, S. H. (1984b). Haemodynamic dose-response effects of intravenous nicardipine in coronary artery disease. *Br. J. clin. Pharmac.*, **18**, 717–724.

Singh, B. N. (1982). Pharmacological basis for the therapeutic applications of slow channel blocking drugs. *Angiology*, **33**, 492–515.

Sorenson, M. B., Bille-Brahe, N. E. & Engell, H. C. (1976). Cardiac output measurement by thermal dilution. Reproducibility and comparison with the dye-dilution technique. *Ann. Surg.*, **183**, 67–72.

Stone, P. H., Antman, E. M., Muller, J. E. & Braunwald, E. (1980). Calcium channel blocking agents in the treatment of cardiovascular disorders. Part II: Hemodynamic effects and clinical applications. *Ann. int. Med.*, **93**, 886–904.

Strashun, A., Horowitz, S. E., Goldsmith, S. J., Teichholz, L. E., Dicker, A., Miceli, K. & Gorlin, R. (1981). Non-invasive detection of left ventricular dysfunction with a portable electrocardiographic gated scintillation probe device. *Am. J. Cardiol.*, **47**, 610–617.

Subramanian, V. B. (1983). *Calcium antagonists in chronic stable angina pectoris*, pp. 161–191. Excerpta Medica, Elsevier Science Publishers BV.

Verma, S. P., Nelson, G. I. C., Jackson, N., Hafizullah, M., Silke, B. & Taylor, S. H. (1984). Haemodynamic variability at rest and following repetitive upright dynamic exercise in coronary heart disease. *Clin. Sci.*, **66**, 52P (Abst).

Wagner, H. N. (1982). The nuclear cardiac probe. *Hospital Practice*, **17**, 163–177.

Weiner, D. A., McCabe, C. H., Cutler, S. S., Creager, M. A., Ryan, I. J. & Klein, M. D. (1983). Efficacy and safety of verapamil in patients with angina pectoris after one year of continuous, high-dose therapy. *Am. J. Cardiol.*, **51**, 1251–1255.

Winer, B. J. (1977). *Statistical principles in experimental design*. 2nd ed., pp. 197–200. New York: McGraw-Hill.

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